Pediatric Focused Safety Review: Levaquin® (levofloxacin)

Pediatric Advisory Committee Meeting
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Outline

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- Pediatric Labeling Changes
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- Drug Use Trends
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Background Drug Information

Levaquin® (levofloxacin)

- **Drug:** Levaquin® (levofloxacin)
- **Formulation:** oral tablets and solution; injectable
- **Therapeutic Category:** fluoroquinolone antibacterial
- **Sponsor:** Ortho McNeil Janssen

Background Drug Information (continued)

Levaquin® (levofloxacin)

Indications:

Adult

- Pneumonia: nosocomial and community acquired
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Skin and skin structure infections: complicated and uncomplicated
- Chronic bacterial prostatitis
- Urinary tract infections: complicated and uncomplicated
- Acute pyelonephritis

Pediatric (≥ 6 months) and adult

- Inhalational anthrax, post-exposure

Background Drug Information (continued) Levaquin® (levofloxacin)

- **Original Market Approval:** December 20, 1996
- **Pediatric Exclusivity Granted:** March 14, 2007
- **PREA labeling changes for this presentation:** May 5, 2008 (post exposure use in pediatrics patients ≥ 6 months for inhalational anthrax)

PREA Pediatric Studies
Levaquin® (levofloxacin)

- The use of levofloxacin in pediatric patients post-exposure to inhalational anthrax is supported by pharmacokinetic modeling comparing adult exposures and exposures achieved in a monkey efficacy study.

- Pharmacokinetic and safety data were reviewed from previous studies in pediatric patients with community acquired pneumonia and acute otitis media.

PREA Pediatric Studies (continued) Levaquin® (levofloxacin)

- The risk-benefit assessment supported administration of levofloxacin to pediatric patients for inhalational anthrax (post-exposure).

- Safety in pediatric patients treated for more than 14 days has not been studied. (Note: dosing for inhalational anthrax is 60 days)

Pediatric Labeling Changes Levaquin® (levofloxacin)

Full prescribing information

2 Dosage and Administration: 2.2 Dosage in Pediatric Patients

- Dosing for pediatric patients 6 months and older for inhalational anthrax

8 Use in Specific Populations: 8.4 Pediatric Use

- Use in pediatric patients for inhalational anthrax (post exposure)
- Risk benefit assessment supports use
- Pharmacokinetics described in pediatric patients age 6 months to 16 years

Relevant Safety Labeling
Levaquin® (levofloxacin)

Boxed Warning:

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis.

Relevant Safety Labeling (continued) Levaquin® (levofloxacin)

5 Warnings and Precautions

5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

LEVAQUIN® is indicated in pediatric patients (≥6 months of age) only for the prevention of inhalational anthrax (post-exposure). An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving LEVAQUIN®.

Inpatient Pediatric Use Levaquin® (levofloxacin)

- Cumulative Y2004-Y2010 and YTD March 2011:
  - About 31.8 million discharges and 22.5 million patients with a hospital billing for oral and injectable Levaquin®.
  - Pediatrics (0-1, 2-5, 6-11, and 12-16 years) accounted for less than 1% of total discharges and patients in each pediatric age group.
- Y2004-2010:
  - Use in all pediatric age groups except adolescents (12-16 years old) remained steady.
  - Use decreased in the adolescent population (-25.5% in the number of discharges).

Source: SDI, IHCarUS. January 2004 through March 2011. Extracted June 2011.

Outpatient Pediatric Use Levaquin® (levofloxacin)

- Cumulative Y2004-Y2010 and YTD March 2011:
  - About 89.9 million prescriptions were dispensed and 50.5 million patients received prescriptions for oral Levaquin®.
  - Pediatrics (0-1, 2-5, 6-11, and 12-16 years) accounted for less than 1% of total prescriptions and patients in each pediatric age group.
- Y2004-Y2010:
  - Use decreased in number of prescriptions dispensed and patients receiving prescriptions for each pediatric age group.

Source: SDI, VONA: National and Total Patient Tracker. January 2004 through March 2011. Extracted June 2011.

Outpatient Pediatric Use (continued) Levaquin® (levofloxacin)

- General Practice/Family Medicine/Doctor of Osteopathy (28%) and Internal Medicine (25%) were the top prescribing specialties.
- Top diagnoses for use:
  - "Urinary Tract Infection NOS" for pediatric patients aged 2-5 years
  - "Cellulitis NOS" for pediatric patients aged 6-11 years and 12-16 years

Source: SDI, VONA and PDDA. January 2004 through March 2011. Extracted June 2011.

Previous PAC Safety Review Levaquin® (levofloxacin) November 18, 2008

- Reviewed pediatric exclusivity studies
- Reviewed adverse event reports since marketing approval (1996)
  - 3 deaths (not suspicious of causal relationship)
  - 100 cases of serious adverse events

Previous PAC Safety Review Levaquin® (levofloxacin) November 18, 2008

- Selected system organ class serious adverse events
  - Musculoskeletal events (n=39)
    - Arthralgia or arthropathy, bone or tendon symptoms, myalgia or myopathy
  - CNS events (n=19)
    - Seizures, abnormal behavior or confusion, hallucinations, panic attacks

- No new safety signals

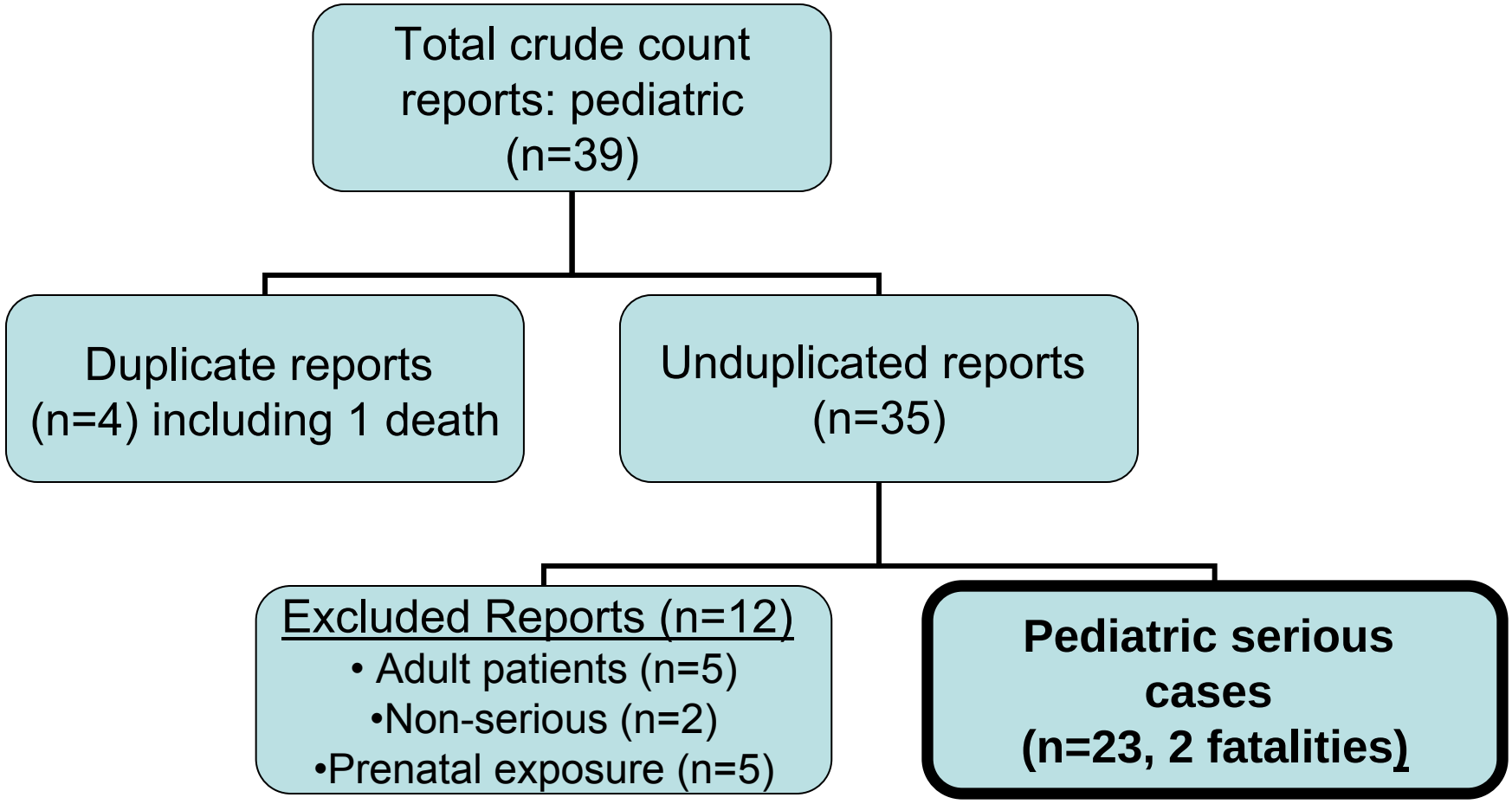
Crude Counts* Levofloxacin Adverse Event Reports (August 28, 2008 to March 31, 2011)

	All reports (US)	Serious** (US)	Death (US)
Adults (≥ 17 yrs.)	4249 (3048)	3681 (2494)	204 (70)
Pediatrics (0-16 yrs.)	39 (24)	34 (19)	3 (2)
Unknown Age (Null values)	727 (610)	680 (566)	43 (29)
All Ages	5015 (3682)	4395 (3079)	250 (101)

*May include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 3414.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Pediatric Case Selection
August 2008 to March 2011



Pediatric Deaths (n=2)
Levaquin® (levofloxacin)

- A report from Japan describes a 15 year old female who took levofloxacin and subsequently died. The report did not contain details such as medical history, history of present illness, concomitant medications, or cause of death.
- 11 year old female with vancomycin and linezolid resistant *Enterococcus faecium* sepsis who had recently undergone allogeneic hematopoietic stem cell transplantation for beta-thalassemia major received levofloxacin. She died of enterococcal sepsis, irreversible graft failure and overwhelming multi-organ failure.

Pediatric Serious Non-Fatal Adverse Event Cases (n=21) Levaquin® (levofloxacin)

- Musculoskeletal (n=9)
- Neurologic (n=4)
- Gastrointestinal (n=2)
- Hypersensitivity Reaction (n=2)
- Cardiovascular (n=1)
- Respiratory (n=1)
- Renal (n=1)
- Overdose (n=1)

Pediatric Serious Non-Fatal Adverse Event Cases
Levaquin® (levofloxacin)

Musculoskeletal (n=9)

- Arthralgia, arthropathy, tendonitis, myalgia, myositis, fibromyalgia, tendon injury, gait abnormality, muscle twitching

Neurologic (n=4)

- Increased intracranial pressure and papilloedema, irritability, serotonin syndrome, auditory hallucination, suicidal and homicidal ideation, cerebrovascular disorder

Unlabeled adverse events are underlined
Each case may have multiple adverse events

Pediatric Serious Non-Fatal Adverse Event Cases
Levaquin® (levofloxacin)

Gastrointestinal (n=2)

- Hypertransaminasemia, vomiting, acute pancreatitis

Hypersensitivity reaction (n=2)

- Drug eruption, urticaria

Cardiovascular (n=1)

- Hypertension, mitral valve incompetence

Unlabeled adverse events are underlined
Each case may have multiple adverse events

Pediatric Serious Non-Fatal Adverse Event Cases
Levaquin® (levofloxacin)

Respiratory (n=1)

- Acute respiratory distress

Renal (n=1)

- Tubulointerstitial nephritis

Overdose (n=1)

- Accidental overdose

Unlabeled adverse events are underlined
Each case may have multiple adverse events

Summary Pediatric Focused Safety Review Levaquin® (levofloxacin)

- This concludes the pediatric focused safety review
- There are no new safety signals
- FDA recommends continuing routine, ongoing post-marketing safety monitoring
- Does the Committee concur?

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